The 'Effects of Transfusion Thresholds on Neurocognitive Outcome of Extremely Low Birth-Weight Infants (ETTNO)' Study: Background, aims, and study protocol

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The 'Effects of Transfusion Thresholds on Neurocognitive Outcome of Extremely Low Birth-Weight Infants (ETTNO)' Study: Background, Aims, and Study Protocol

ETTNO Investigators[1]

Key Words
Infant, preterm · Anemia of prematurity, treatment · Transfusion · Randomized controlled trial

Abstract
Background: Infants with extremely low birth weight uniformly develop anemia of prematurity and frequently require red blood cell transfusions (RBCTs). Although RBCT is widely practiced, the indications remain controversial in the absence of conclusive data on the long-term effects of RBCT. ***Objectives:*** To summarize the current equipoise and to outline the study protocol of the 'Effects of Transfusion Thresholds on Neurocognitive Outcome of extremely low birth-weight infants (ETTNO)' study. ***Methods:*** Review of the literature and design of a large pragmatic randomized controlled trial of restrictive versus liberal RBCT guidelines enrolling 920 infants with birth weights of 400–999 g with long-term neurodevelopmental follow-up. ***Results and Conclusions:*** The results of ETTNO will provide definite data about the efficacy and safety of restrictive versus liberal RBCT guidelines in very preterm infants.

[1] The names and affiliations of the ETTNO Investigators are listed in the Appendix.

Introduction

Infants with extremely low birth weight uniformly develop anemia of prematurity and frequently require multiple red blood cell transfusions (RBCTs) during neonatal intensive care [1–3]. The criteria currently applied to indicate RBCTs in this population are based on expert opinion rather than evidence and there is a lack of conclusive data on long-term effects of RBCT practices. Transfusing infants to improve oxygen-carrying capacity and restricting RBCT to avoid transfusion-associated risks and costs may both potentially impair long-term development.

Potential Risks and Benefits of RBCTs

Although RBCTs are a universally accepted part of the treatment of preterm infants, recent reviews concluded that there are insufficient data on the long-term effects of RBCT practices [4, 5]. In the absence of uniformly accepted physiologic or evidence-based RBCT criteria, RBCT practices vary greatly between neonatal intensive-care units [1, 6–10].

RBCTs may be associated with retinopathy of prematurity [11–13], bronchopulmonary dysplasia [14, 15],

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acute pulmonary deteriorations [16], necrotizing enterocolitis [17–19], intraventricular hemorrhage [20], and increased mortality [21] although these associations require cautious interpretation because of the retrospective and observational character of the underlying studies [22]. RBCTs are also associated with a minute residual risk of transmission of infectious agents [23]. Implementing RBCT guidelines effectively reduces the number of RBCTs administered to preterm infants [24, 25], and 'restrictive' RBCT guidelines are feasible in very low birthweight infants and may result in very low numbers and low cumulative volumes of RBCTs [26].

However, reducing RBCTs by accepting low hemoglobin concentrations carries the risk of an at least temporarily insufficient oxygen transport to vital organs and impaired outcome [27].

In a recent randomized trial of restrictive versus liberal RBCT guidelines in 103 infants with birth weights of 500–1,300 g, restrictive RBCT guidelines were associated with a marginally increased incidence of apnea [28]. The study reported an increased incidence of brain injury (intraventricular hemorrhage grade 4 or periventricular leukomalacia) with restrictive RBCT guidelines. This study was criticized because (a) the primary endpoint for sample size determination was the number of transfusions and not a clinically relevant outcome parameter, (b) the combined outcome of intraventricular hemorrhage grade 4 or periventricular leukomalacia had not been a predefined outcome measure, (c) intraventricular hemorrhage usually occurs at a time when infants had not yet been enrolled into that study, (d) there was an excess of male patients in the restrictive-transfusion group and male infants tend to have poorer outcomes, (e) only 52% of the patients had a late cranial ultrasound, despite the latter being required to assess the true incidence of periventricular leukomalacia [29–31]. In contrast to the initial findings, long-term follow-up showed poorer results in measures of associative verbal fluency, visual memory, and reading in the liberally transfused group [32] and liberally transfused girls had the most prominent abnormalities on magnetic resonance imaging [33]. Again, these latter results have to be interpreted with caution because only about half of the patients initially enrolled in the trial completed these follow-up examinations.

In another recent randomized trial of restrictive versus liberal RBCT guidelines, the Premature Infant in Need of Transfusion (PINT) Trial, 451 infants with a birth weight <1,000 g were enrolled. Restrictive RBCT guidelines were associated with fewer transfusions but there were no differences in the primary outcome, death or survival with retinopathy of prematurity ≥3rd degree, bronchopulmonary dysplasia, or brain injury on ultrasound [34]. Nor was there a statistically significant difference in the incidence of death or severe adverse neurodevelopmental outcome [35]. However, post-hoc analyses showed that the proportion of infants with cognitive delay defined as a Mental Developmental Index (MDI) <85 was lower and the mean MDI was higher in the liberal-transfusion group, raising concern that restrictive transfusion guidelines may result in impaired neurodevelopment. Notably, maintaining higher hemoglobin concentrations appeared to be less costly [36].

This study was criticized for the fact that the mean difference in hemoglobin levels between the two treatment groups was only marginal (1 g/dl) and that the mean hemoglobin levels were high in both groups (10 vs. 11 g/dl) and may not reflect the range of RBCT guidelines currently proposed [37].

Open Questions

There is insufficient evidence to decide whether preterm infants should be treated according to liberal or restrictive RBCT guidelines [4, 5]. The long-term safety and efficacy of 'restrictive' RBCT practices can only be evaluated in an adequately powered, large, randomized controlled trial with long-term neurodevelopmental follow-up and with a sufficient difference in mean hemoglobin levels between both treatment arms to reflect the range of RBCT guidelines currently applied. Such a trial may help to improve survival without neurodevelopmental impairment in preterm infants.

Summary of Study

The Effects of Transfusion Thresholds on Neurocognitive Outcome of Extremely Low Birth-Weight Infants (ETTNO) study is an observer-blinded randomized controlled clinical trial. Nine hundred and twenty infants of 400–999 g birth weight will be randomized to restrictive or liberal transfusion trigger thresholds between 48 and 72 h of life, stratified by center and birth weight (400–749 g/750–999 g) (table 1). Sample size calculations were based on a χ^2 test assuming a power of 80%, a two-sided significance level of 5%, an incidence of death or major neurodevelopmental impairment (where cognitive delay is defined as MDI <85) of 61% versus 51% in the restrictive-threshold and the liberal-threshold group, respec-

Table 1. ETTNO transfusion thresholds

Time after randomization	Hematocrit, %			
	restrictive RBCT thresholds		liberal RBCT thresholds	
	critical	noncritical	critical	noncritical
3–7 days of age	<34	<28	<41	<35
8–21 days of age	<30	<24	<37	<31
>21 days of age	<27	<21	<34	<28

'Critical' refers to state of health and is defined as the presence of any of the following: (1) requirement of mechanical ventilation (any mode, excluding continuous positive airway pressure), (2) requirement of continuous positive airway pressure with FiO_2 >0.25 for >12 h per 24 h, (3) patent ductus arteriosus requiring therapy, (4) more than 6 apneas that require stimulation per 24 h, or more than 4 desaturations to SpO_2 <60% per 24 h despite methylxanthines and continuous positive airway pressure and (5) acute sepsis or acute necrotizing enterocolitis requiring inotropic or vasopressor support.

tively, based on the reported outcome data of the PINT study [35].

The assigned RBCT guidelines will be applied until discharge home from hospital. Both, the restrictive and the liberal RBCT guidelines to be compared in this trial reflect current clinical practice [5, 6, 8, 26, 38–41]. These RBCT guidelines will result in a clinically relevant difference in mean hemoglobin concentrations between both treatment groups of about 2 g/dl and will therefore improve recognition of any effect of transfusion trigger thresholds on neurocognitive outcome compared with the above referenced PINT trial [34, 35].

The primary outcome, death or neurodevelopmental impairment, will be determined at 24 months of age, corrected for prematurity. Funding for longer-term follow-up until 5.5 years of age will be sought. Neurodevelopmental impairment will be defined as any of the following: cognitive delay defined as MDI score of the *Bayley Scales of Infant Development* (2nd edition) <85, cerebral palsy, or severe visual or hearing impairment. In the intention-to-treat population of all randomized patients in whom the primary outcome is ascertained, the primary outcome variable will be analyzed by logistic regression with factors treatment, center, and birth weight category at a two-sided significance level of 5%.

The study has been approved by the leading ethics committee at the University of Tübingen, Germany, and by the German Regulatory Authority (Paul-Ehrlich-Institut). Written informed consent will be required from parents or caretakers.

Recruitment began in August 2011 and units are invited to participate. The results of ETTNO will provide definite data about the efficacy and safety of restrictive versus liberal RBCT guidelines in very preterm infants.

Collaborations will be sought with other groups to perform individual patient data meta-analyses to (a) verify the effect of different levels of transfusion trigger thresholds on neurodevelopmental outcome and (b) analyze the impact of transfusion triggers on less frequently observed complications of prematurity, such as severe retinopathy, severe chronic lung disease, necrotizing enterocolitis and others.

Appendix

The ETTNO Investigators

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Identification

EudraCT-No.: 2010-021576-28. ClinicalTrials.gov Identifier: NCT01393496.

Disclosure Statement

All ETTNO Investigators confirmed that they have no conflict of interest to declare.

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